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Global systematic review of primary immunodeficiency registries

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REVIEW



Global systematic review of primary immunodeficiency registries

Hassan Abolhassani^{a,b}, Gholamreza Azizi^c, Laleh Sharifi^{a,ab}, Reza Yazdani^a, Monireh Mohsenzadegan^a, Samaneh Delavari^{a,ac}, Mahsa Sohani^a, Paniz Shirmast^a, Zahra Chavoshzadeh^d, Seyed Alireza Mahdavian^e, Arash Kalantari^f, Marzieh Tavakoli^c, Farahzad Jabbari-Azad^g, Hamid Ahanchian^g, Tooba Momen^h, Roya Sherkatⁱ, Mahnaz Sadeghi-Shabestari^j, Soheila Aleyasin^k, Hossein Esmaeilzadeh^k, Waleed Al-Herz^{l,m}, Ahmed Aziz Bousfiha^{n,o,p}, Antonio Condino-Neto^{q,r}, Mikko Seppänen^{s,t,u}, Kathleen E. Sullivan^{v,w}, Lennart Hammarström^b, Vicki Modell^x, Fred Modell^x, Jessica Quinn^x, Jordan S. Orange^{x,y} and Asghar Aghamohammadi^{a,z,aa}

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ABSTRACT

Introduction: During the last 4 decades, registration of patients with primary immunodeficiencies (PID) has played an essential role in different aspects of these diseases worldwide including epidemiological indexes, policymaking, quality controls of care/life, facilitation of genetic studies and clinical trials as well as improving our understanding about the natural history of the disease and the immune system function. However, due to the limitation of sustainable resources supporting these registries, inconsistency in diagnostic criteria and lack of molecular diagnosis as well as difficulties in the documentation and designing any universal platform, the global perspective of these diseases remains unclear.

Areas covered: Published and unpublished studies from January 1981 to June 2020 were systematically reviewed on PubMed, Web of Science and Scopus. Additionally, the reference list of all studies was hand-searched for additional studies. This effort identified a total of 104614 registered patients and suggests identification of at least 10590 additional PID patients, mainly from countries located in Asia and Africa. Molecular defects in genes known to cause PID were identified and reported in 13852 (13.2% of all registered) patients.

Expert opinion: Although these data suggest some progress in the identification and documentation of PID patients worldwide, achieving the basic requirement for the global PID burden estimation and registration of undiagnosed patients will require more reinforcement of the progress, involving both improved diagnostic facilities and neonatal screening.

KEYWORDS

Primary immunodeficiencies; burden of disease; ethnicity; prevalence; molecular diagnosis

1. Introduction

Primary immunodeficiencies (PID) are described as heterogeneous diseases with a shortcoming in the development and

function of the immune system [1,2]. PID patients usually suffer from more severe and repeated infections [3], however, dysregulation of immunity predisposes the immunodeficient

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Article highlights

- Globally, there are more than 6 million children under the age of 15 years die annually despite substantial progress in vaccination, adequate nutrition, exclusive breastfeeding, reduction of household air pollution, providing safe water and food and adequate sanitation and hygiene worldwide. Leading causes of death in children include severe infectious diseases (i.e. pneumonia and diarrhea) which could affect mainly those with underlying immune system defects. Although vaccines are available for some of the most deadly childhood diseases, such as measles, polio, diphtheria, tetanus, and pertussis, pneumonia due to *Haemophilus influenzae type B* and *Streptococcus pneumoniae* and diarrhea due to rotavirus, they cannot protect immunodeficient children from illness and death.
- PIDs are a heterogeneous group of disorders, and no single assay at present will identify all forms of PID, necessitating a challenge of newborn screening paradigms. Therefore, there is no correct estimation of the global PID prevalence in different regions and ethnicities.
- This is the first systematic review on PID patients' registries worldwide summarizing the differences in the distribution and properties of immune system disorders. The authors' systematic review included 104614 patients registered in 80 countries from five continents.
- The authors found that PID patients are at significant risk of misdiagnosis and misclassification in Asia and Africa, the continents with the highest report of childhood death. The findings provide important new insights into the genetic diagnosis of diagnosed patients in different registries and entitlement to molecular approaches worldwide and highlight the need to continue to promote global frameworks for identification of monogenic causes as well as other molecular or environmental modifying factors.
- PID burden has been critically underestimated in policymaking and usually, it has been distributed in different categories—mainly infectious diseases, diseases of the blood-forming organs, and neoplasms—because of an inaccurate diagnosis, multiple organ involvement, and different phenotypes. Governments, policymakers, and clinicians must work to develop and enforce measures for early diagnosis of PID, and promote access to appropriate management based on the type of the disease. Existing international frameworks must continue to implement correct clinical, immunological and genetic picture of the PID.

patients to lymphoproliferation, atopy, autoimmunity and malignancy [1,4]. Since the first report of PID in 1952, we have encountered an explosion of knowledge in this field with recognition of more than 400 genetic defects that are connected to even more PID phenotypes [1], that make this group of diseases an independent pursuit within biomedicine.

Presentation of PID varies from potentially benign forms such as IgA deficiency to catastrophic types such as severe combined immunodeficiency (SCID). Complex medical features and the necessity for lifelong and resource-consuming treatments in many patients underscores the importance of qualified epidemiological data in decision making and PID management. Although epidemiological research in this field faces a variety of difficulties due to the novelty of PID and its rarity [5], national and international collaborations help to advance translational research and improve the management and therapeutic strategies [6,7].

Most of the prevalence estimations have been based on selected populations such as tertiary hospitals, or single-center registries. Reports from several PID registries in different countries show a prevalence of 1:8500 to 1:100000 for symptomatic patients [5,8–14]. However, it has been generally accepted that PID is under-diagnosed and under-reported.

Furthermore, measurement of the burden of PID is restricted owing to insufficient recording and reporting. In 1981, the registration of patients was first advanced within countries initiated by Japan [15], followed by intracontinental registration efforts such as by the Latin American Society for Immunodeficiencies (LASID) in 1993 [16] and even global initiatives advanced by the Jeffrey Modell Foundation (JMF) in 2011 [17].

Although it has been suggested that obtaining incidence rates from local networks and national registries with proper data documentation could be a way to predict incidence for larger populations, this method cannot create a valid picture of PID in other populations as the prevalence of particular PID varies in different ethnic groups [18]. To consider this issue, several larger networks have been formed to collect the data from independent countries and diverse regions such as the European Society for Immunodeficiencies (ESID), LASID and The United States Immunodeficiency Network (USIDNET) databases [16,19]. However, obvious discrepancies among different online sources and published documents create challenges in measuring accurate global disease burdens. This review is designed to systematically consider all available evidence regarding PID registries and present the frequencies of these diseases in 80 countries and all well-known international PID networks. The overarching objective is to provide deeper insights into the epidemiology of PID by comparing worldwide the prevalence, clinical and molecular diagnoses, and predisposing factors in different populations.

2. Methods

Detailed methods, including search strategy for systematic review, study selection, data extraction and quality assessment are described in the Supplementary Method and Figure S1. The study was approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran.

3. Results

3.1. Asia

A total of 15939 PID patients from 18 nationwide registries were surveyed in Asia (Table 1) representing a diverse distribution of PID in these countries based on PID prevalence (Figure 1), parental consanguinity (Figure 2), proportions of PID categories (Figure 3), gender ratio (Figure 4) and genetic diagnosis (Figure 5). The first PID registry was reported in Japan, which included 497 patients [15] and the most recent data from Japan has been reported in 2011 by Ishimura et al., in which a total of 1240 patients have been registered with a prevalence of 2.3 per 100000 inhabitants. Predominantly antibody deficiencies (41.2%) were the most frequent type of PID, followed by congenital defects of phagocyte (18.5%) and other well-defined immunodeficiency syndromes (16%). Bruton's tyrosine kinase (BTK) deficiency was the most prevalent genetic defect amongst Japanese PID patients. Common variable immunodeficiency (CVID) and selective IgA deficiency (SIgAD) comprise only 11% and 4% of the PID patients, respectively [14].

Table 1. The frequency of diagnosed primary immunodeficiency (PID) cases in the world and percentage of Predominantly antibody deficiencies (PAD), immunodeficiencies affecting cellular and humoral immunity (CID), congenital defects of phagocyte number or function, complement deficiencies and other PIDs (including syndromic CID, diseases of immune dysregulation, defects in intrinsic and innate immunity, autoinflammatory disorders and PID phenocopies).

Continent	Rank	Reigon/Country [ref]	Population at year of report	Registered Patients	Year of report	PAD (%)	CID (%)	Phagocytic defects (%)	Complement deficiency (%)	Other PIDs (%)	Genetic diagnosis (%)	Gender ratio M/F	Consanguinity (%)
Asia	1	Qatar [39]	2250000	131	2013	23.7	22.9	12.2	-	41.2	48 (36.6)	1.3	61.1
	2	Iran [42,5,26,93]	80260000	3056	2018	29.5	17.3	16.6	2.0	34.6	1014 (33.1)	1.5	60.1
	3	Oman [44]	4425000	140	2016	20.7	17.8	35.0	3.5	23.0	-	1.6	76.0
	4	Kuwait [20,38,39,92]	4137000	314	2019	17.8	53.5	6.4	7.0	15.3	217 (69.0)	1.1	78.0
	5	Turkey [2,29,30]	84,339,067	6392	2020	69.1	5.7	5.1	0.8	19.3	-	1.6	14.3
	6	Turkey (Based on ESID registry) [58]	76670000	1837	2014	-	-	-	-	-	-	-	-
	7	Saudi Arabia [32,33]	31560000	502	2015	12.3	59.7	9.4	5.8	12.8	152 (30.2)	1.1	75.0
	8	Japan [14,15]	127700000	1240	2011	41.2	10.8	18.5	2.6	26.9	46 (3.7)	2.3	-
	9	China [27,28]	1386000000	2487	2018	27.9	15.9	14.6	7.5	34.1	1139 (45.7)	4.4	-
	10	Taiwan [13]	23162123	215	2011	25.1	15.8	11.6	7.0	40.5	109 (50.6)	2.3	-
	11	Hong Kong [41-43]	7100000	180	2014	42.7	4.2	15.3	3.4	34.4	107 (59.4)	1.6	-
	12	Korea [34]	50200000	152	2012	53.3	10.5	28.9	-	7.3	-	3.6	-
	13	Malaysia [43,45]	29710000	150	2014	40.4	15.4	17.3	-	26.9	-	2.1	52.6
	14	Thailand [46]	67800000	67	2009	52.2	32.8	9.0	-	6.0	10 (14.9)	1.9	9.0
	15	India [35,36]	1336000000	778	2019	17.1	8.6	21.3	1.0	52.0	313 (40.2)	-	19.4
	16	Singapore [48]	4115000	39	2003	40.0	15.4	15.4	25.6	3.6	6 (15.3)	1.2	-
	17	Jordan [47]	8809000	53	2014	100	-	-	-	-	-	2.3	-
	18	Bangladesh [50]	155700000	13	2012	100	-	-	-	-	-	5.5	-
	19	UAE [49]	9397599	30	2018	-	-	-	-	-	-	-	-
Oceania	1-18	Asia (Based on JMF registry) [17,88]	4463000000	8022	2018	-	-	-	-	-	-	-	-
	1-18	Total Asia (Based on total registries)	464452067	15939	2020	41.9	20.4	13.8	3.5	20.3	3161 (25.9)	2.2	20.8
	19-20	Australia and New Zealand [9,12]	24885000	1209	2007	77.4	8.9	3.2	5.9	4.6	223 (18.4)	1.1	-
	19-20	Total Australia (Based on JMF registry) [17,88]	24600000	1876	2018	-	-	-	-	-	-	-	-
	19-20	Total Oceania (Based on published registries)	42669777	1876	2020	77.4	8.9	3.2	5.9	4.6	223 (11.8)	1.1	-
	21	Tunis [53]	11270000	710	2015	17.7	28.6	25.4	0.4	27.9	98 (13.8)	1.4	58.2
	22	Morocco [49,56,98]	32520000	424	2014	22.7	24.1	15.1	3.1	35.0	22 (5.1)	1.1	43.2
	23	Libya [49]	6408742	106	2018	-	-	-	-	-	-	-	-
	24	Algeria [49,98]	41063753	600	2018	-	-	-	-	-	11 (1.8)	-	-
	25	Egypt [49,54,55]	95690000	476	2016	18.0	29.6	13.2	1.2	37.5	106 (22.2)	1.4	79.7
Africa	26	Sout Africa [21,51,52]	52260000	168	2011	50.6	25.0	5.4	4.2	14.8	13 (7.7)	1.5	1.1
	27	Sudan [49]	2166323	72	2018	-	-	-	-	-	-	-	-
	21-27	Total Africa (Based on Maghreb registries) [49]	1246504865	4509	2018	-	-	-	-	-	-	-	-
	21-27	Total Africa (Based on JMF registry) [17,88]	1246504865	1836	2018	-	-	-	-	-	-	-	-
	21-27	Total Africa (Based on published registries)	1339849038	4509	2020	22.0	27.4	17.7	1.6	30.9	250 (5.5)	1.3	54.9
	28	Ireland [72]	318041	66	2015	39.4	4.5	12.1	28.8	15.2	22 (33.3)	0.88	-
	29	Norway [10,73]	4450000	372	2000	50.8	3.5	6.7	21.0	18.0	33(8.8)	1.2	-
	30	Finland [2,58]	5171000	48	2000	71.1	8.3	10.4	4.2	6.0	-	-	-
	30	Finland [75]	5503000	132	2017	100	-	-	-	-	-	1.08	-
	31	Croatia [2,58,76]	4100000	226	2019	63.3	6.7	-	30.0	-	80 (35.3)	-	-
	31	Croatia (Based on ESID registry) [58]	4247000	24	2014	-	-	-	-	-	-	-	-
	32	Serbia (Based on ESID registry) [58]	7131000	88	2014	-	-	-	-	-	-	-	-
	33	Slovakia (Based on ESID registry) [58]	5416000	63	2014	-	-	-	-	-	-	-	-
	33	Slovakia (Based on JMF registry) [76]	5400000	227	2019	41.0	6.5	6.0	14.5	32.0	95 (41.8)	-	-
	34	Estonia (Based on JMF registry) [76]	1300000	99	2019	41.0	6.5	6.0	14.5	32.0	10 (10.1)	-	-
	34	Estonia (Based on ESID registry) [58]	1316000	42	2014	-	-	-	-	-	-	-	-

(Continued)

Table 1. (Continued).

Continent	Rank	Reigon/Country [ref]	Population at year of report	Registered Patients	Year of report	PAD (%)	CID (%)	Phagocytic defects (%)	Complement deficiency (%)	Other PIDs (%)	Genetic diagnosis (%)	Gender ratio M/F	Consanguinity (%)
	35	Belarus (Based on ESID registry) [58]	9475000	67	2014	-	-	-	-	-	-	-	-
	35	Belarus (Based on JMIF registry) [76]	9400000	436	2019	41.0	6.5	6.0	14.5	32.0	250 (57.3)	-	-
	36	Ukraine (Based on ESID registry) [58]	45270000	33	2014	-	-	-	-	-	-	-	-
	37	Romania (Based on ESID registry) [58]	19950000	11	2014	-	-	-	-	-	-	-	-
	37	Romania (Based on JMIF registry) [76]	19400000	222	2019	41.0	6.5	6.0	14.5	32.0	45 (20.2)	-	-
	38	Lithuania (Based on ESID registry) [58]	2943000	8	2014	-	-	-	-	-	-	-	-
	38	Lithuania (Based on JMIF registry) [76]	2800000	172	2019	41.0	6.5	6.0	14.5	32.0	20 (11.6)	-	-
	39	Austria [2,58,76]	8700000	312	2019	67.6	26.8	2.8	1.4	1.4	100 (32.0)	-	-
	39	Austria (Based on ESID registry) [58]	8505000	105	2014	-	-	-	-	-	-	-	-
	39	Austria (Based on ESID registry) [58]	10240000	64	2000	64.1	10.9	17.2	4.7	3.1	-	-	-
	40	Belgium [2,58]	11180000	258	2014	-	-	-	-	-	-	-	-
	40	Belgium (Based on ESID registry) [58]	9600000	730	2019	22.2	-	14.5	63.3	-	140 (19.1)	-	-
	41	Hungary [2,58,76]	9877000	404	2014	-	-	-	-	-	-	-	-
	41	Hungary (Based on ESID registry) [58]	10280000	518	2000	78.0	8.1	1.2	11.5	1.2	190 (36.6)	-	-
	42	Czech [2,58,76]	10510000	259	2014	-	-	-	-	-	-	-	-
	42	Czech (Based on ESID registry) [58]	64990000	6602	2019	42.8	17.4	18.4	0.5	20.9	2859 (43.3)	1.39	15.0
	43	France [2,58,61,62]	66130000	5426	2014	-	-	-	-	-	-	-	-
	43	France (Based on ESID registry) [58]	39387000	2030	2001	69.1	8.3	4.6	10.2	7.8	-	-	-
	44	Spain [2,18,58]	46510000	2211	2014	-	-	-	-	-	-	-	-
	44	Spain (Based on ESID and REDIP registries) [58]	82790000	2453	2019	56.6	7.2	8.1	1.7	26.4	893 (36.4)	1.24	8.0
	45	Germany [68,69]	81200000	1981	2014	-	-	-	-	-	-	-	-
	45	Germany (Based on ESID registry) [58]	11150000	147	2014	20.4	38.8	17.0	1.4	22.4	-	2.1	1.3
	46	Greece [2,58]	11150000	202	2014	-	-	-	-	-	-	-	-
	46	Greece (Based on ESID registry) [58]	66040000	4758	2018	59.6	9.9	4.8	9.2	16.5	1204 (25.3)	0.98	2.9
	47	UK [11,63,65]	64600000	2229	2014	-	-	-	-	-	-	-	-
	47	UK (Based on ESID registry) [58]	3997000	115	2005	46.1	12.2	9.6	27.8	4.3	-	1.5	-
	48	Ireland [66]	4638000	107	2014	-	-	-	-	-	-	-	-
	48	Ireland (Based on ESID registry) [58]	10250000	208	2000	76.9	6.3	3.8	6.7	6.3	-	-	-
	49	Portugal [2,58]	10430000	76	2014	-	-	-	-	-	-	-	-
	49	Portugal (Based on ESID registry) [58]	10230000	2727	2019	43.7	13.8	21.8	0.6	20.1	-	0.61	-
	50	Sweden [70,71]	9645000	92	2014	-	-	-	1.6	12.7	-	-	-
	50	Sweden (Based on ESID registry) [58]	55260000	797	1983	66.6	14.2	4.9	-	-	-	-	-
	51	Italy [2,22,58-60]	60780000	1275	2014	-	-	-	-	-	-	-	-
	51	Italy (Based on ESID registry) [58]	146600000	161	2000	59.6	29.8	6.2	-	4.4	-	-	-
	52	Russia [2,58]	144100000	204	2014	-	-	-	-	-	-	-	-
	52	Russia (Based on ESID registry) [58]	8235000	348	2015	61.5	11.5	8.9	4.6	13.5	95 (27.3)	1.0	2.3
	53	Switzerland [2,58]	8140000	352	2014	-	-	-	-	-	-	-	-
	53	Switzerland (Based on ESID registry) [58]	2064000	272	2019	17.4	8.5	11.7	28.3	34.1	155 (57.0)	1.4	-
	54	Slovenia [2,58,76]	2061000	16	2014	-	-	-	-	-	-	-	-
	54	Slovenia (Based on ESID registry) [58]	38430000	4099	2016	70.2	1.8	8.5	1.6	17.9	-	-	-
	55	Poland [67]	38440000	690	2014	-	-	-	-	-	-	-	-
	55	Poland (Based on ESID registry) [58]	6570000	294	2002	31.6	26.5	18.0	16.3	7.6	-	2.0	-
	56	Israel [2,58]	8216000	4	2014	-	-	-	-	-	-	-	-
	56	Israel (Based on ESID registry) [58]	16900000	743	2015	60.6	8.5	8.6	1.5	20.8	-	-	-
	57	Netherlands [2,58]	16900000	743	2014	-	-	-	-	-	-	-	-
	57	Netherlands (Based on ESID registry) [58]	5749000	179	2017	100	-	-	-	-	3(1.6)	1.1	-
	58	Denmark [74]	9981000	100	2019	41.0	6.5	6.0	14.5	32.0	10 (10.0)	-	-
	59	Azerbaijan [76]	6900000	143	2019	41.0	6.5	6.0	14.5	32.0	35 (24.4)	-	-
	60	Bulgaria [76]	74100000	40,223	2018	-	-	-	-	-	-	-	-
	28-60	Europe (Based on JMIF registry) [17,88]											

(Continued)

Table 1. (Continued).

Continent	Rank	Reigon/Country [ref]	Population at year of report	Registered Patients	Year of report	PAD (%)	CID (%)	Phagocytic defects (%)	Complement deficiency (%)	Other PIDs (%)	Genetic diagnosis (%)	Gender ratio M/F	Consanguinity (%)
America	28–60	Europe (Based on new ESID registry) [100]	747632000	33,503	2020	51.9	9.9	7.9	5.0	25.3	-	1.23	-
	28–60	Europe (Based on total registries)	747632000	40,223	2020	53.9	11.3	9.0	13.0	12.6	6239 (15.5)	0.7	3.4
	61	Argentina [80,81,83–85]	44270000	2730	2018	68.4	10.4	3.9	1.0	16.3	-	-	-
	62	Brazil [23,80,81,83–87]	209300000	1879	2018	60.8	9.9	7.3	2.9	19.1	-	1.4	-
	63	Chile [80,81,83–85]	18050000	116	2018	43.0	23.7	6.8	1.8	24.7	-	-	-
	64	Colombia [80,81,83–85]	49070000	1073	2018	46.2	21.4	8.3	2.8	21.3	-	4.0	-
	65	Costa rica [80,81,83–85]	4453000	193	2007	24.9	18.1	4.1	0.5	52.4	-	-	-
	66	Cuba [80,81,83–85]	11480000	55	2018	-	-	-	-	-	-	-	-
	67	Guatemala [80,81,83–85]	16910000	6	2018	-	-	-	-	-	-	-	-
	68	Honduras [80,81,83–85]	9265000	58	2018	32.4	16.2	10.8	0	40.6	-	-	-
	69	Mexico [83,84]	129200000	1744	2018	36.3	15.0	14.0	1.5	33.2	-	2.1	11
	70	Paraguay [80,81,83–85]	6811000	115	2018	38.5	10.3	33.3	0	17.9	-	-	-
	71	Peru [80,81,83–85]	32170000	204	2018	17.6	17.6	5.9	11.8	47.1	-	-	-
	72	Rep Dominican [80,81,83–85]	10770000	5	2018	-	-	-	-	-	-	-	-
	73	Uruguay [80,81,83–85]	3340000	95	2007	58.9	8.4	3.2	9.5	20.0	-	-	-
	74	Venezuela [80,81,83–85]	27690000	22	2007	40.9	9.1	4.5	9.1	36.4	-	-	-
	75	El salvador [80,81,83–85]	6375000	5	2018	-	-	-	-	-	-	-	-
	76	Bolivia [80,81,83–85]	11673000	19	2020	-	-	-	-	-	-	-	-
	77	Panama [80,81,83–85]	3454000	59	2007	55.9	15.3	8.5	3.4	33.8	-	-	-
	78	Ecuador [24]	17643000	45	2020	-	-	-	-	-	-	-	-
Globe	61–78	Latin America (Based on LASID registry publication) [80,81,83–85]	468000000	5695	2015	62.5	9.4	7.6	3.4	17.1	-	-	-
	61–78	Latin America (Based on LASID registry website) [24]	652012001	8146	2018	52.0	9.0	9.0	3.0	27.0	1467(18.0)	-	-
	61–78	Latin America (Based on JMF registry) [17,88]	652012001	8793	2018	-	-	-	-	-	-	-	-
	79	USA (USIDNET Website) [77]	331002000	5484	2020	49.1	20.1	12.0	0.5	18.3	2512 (45.8)	1.45	-
	79	USA (Based on JMF registry) [17,88]	306800000	30227	2018	57.1	4.3	4.0	2.1	32.5	-	-	-
	80	Canada (Based on JMF registry) [17,88]	37060000	3047	2018	-	-	-	-	-	-	-	-
	61–80	America (Based on total registries)	1001000000	42067	2020	56.0	5.2	5.0	2.3	31.3	3979 (9.4)	2.5	0.5
	1–80	World (Based on JMF registry) [17,88]	7700000000	94024	2018	45.1	6.1	5.2	4.7	38.9	-	1.3	-
	1–80	World (Based on total registries)	7800000000	104614	2020	51.9	10.8	8.3	6.6	22.1	13852 (13.2)	1.5	6.2

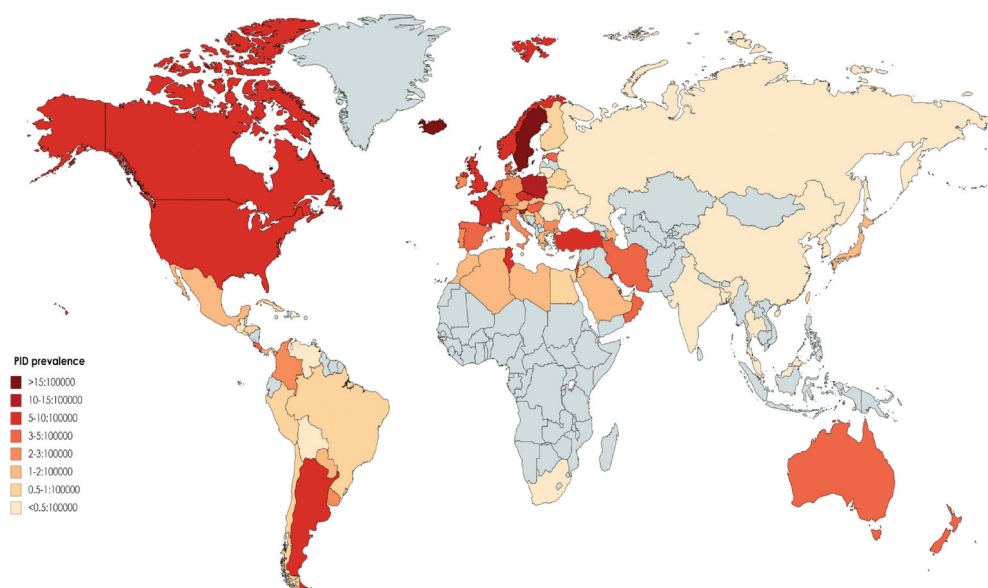


Figure 1. Distribution of primary immunodeficiency prevalence in the world based on the number of reported patients per 100000 individuals (Gray color represents countries without registry or without published report).

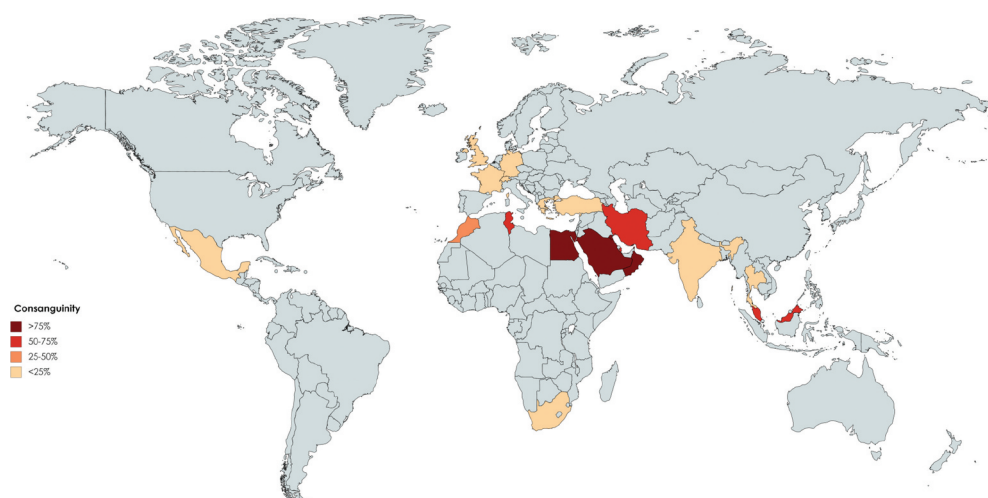


Figure 2. Distribution of parental consanguinity among different registries of patients with primary immunodeficiency in the world. (Gray color represents countries without registry or without appropriate report).

Iran was the second country in Asia to report the national PID registry published in 2002 [25], with updated data reported in 2018 [4,26]. In total, 3056 PID patients were reported by the Iranian PID network centers thus describing the largest cohort of patients in Asia and the fifth-largest national cohort of patients globally. The prevalence of PID has been estimated to be around 3.9 per 100000 in the population. Predominantly antibody deficiencies (29.5%) and combined immunodeficiency (17.3%) were the most common PID subcategories. SCID was reported as the most frequent specific disorder (21.1%) followed by CVID (14.9%). Molecular diagnosis was achieved in 33.1% of registered patients in this highly consanguineous cohort (60.1%).

Wang et al. published the first registry of 201 Chinese PID patients emanating from a single center in 2011. During recent years, efforts of different centers from seven main cities in the mainland China registered 2487 patients (the second-largest PID cohort in Asia, estimated prevalence of <0.2:100000, 45.7% genetically diagnosed). Predominantly antibody deficiency disease was the leading PID type with 27.9% of all patients. Agammaglobulinemia was the most common specific PID disorder and mutations in the *BTK* gene were the most common genetic defect identified in the Chinese PID population (29%) [27,28].

Kilik et al. in 2013 have reported registry data of 1435 immunodeficient patients from Turkey [29]. However, updated data

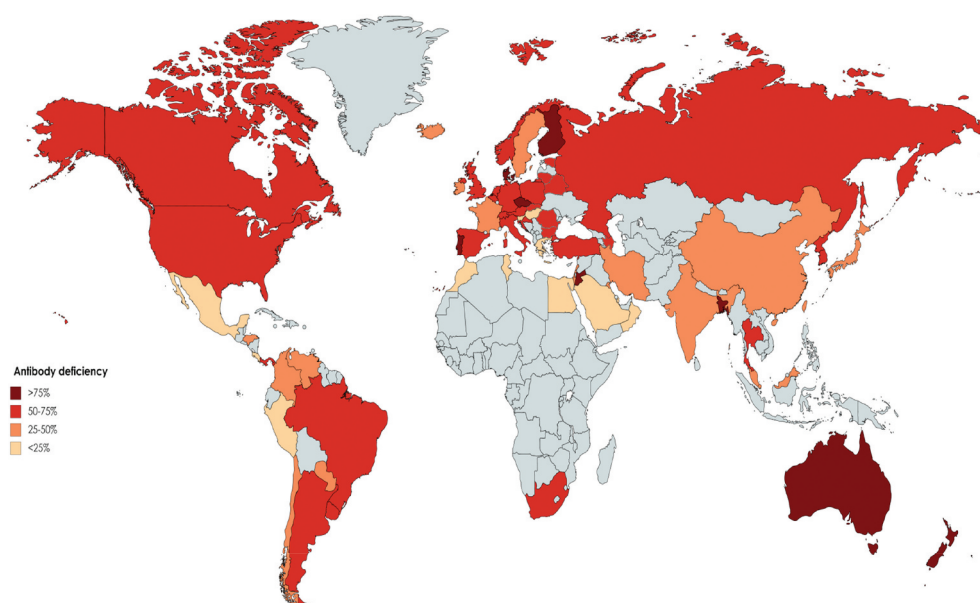


Figure 3. Proportion of predominant antibody deficiencies among different registries of patients with primary immunodeficiency in the world. (Gray color represents countries without registry or without appropriate report).

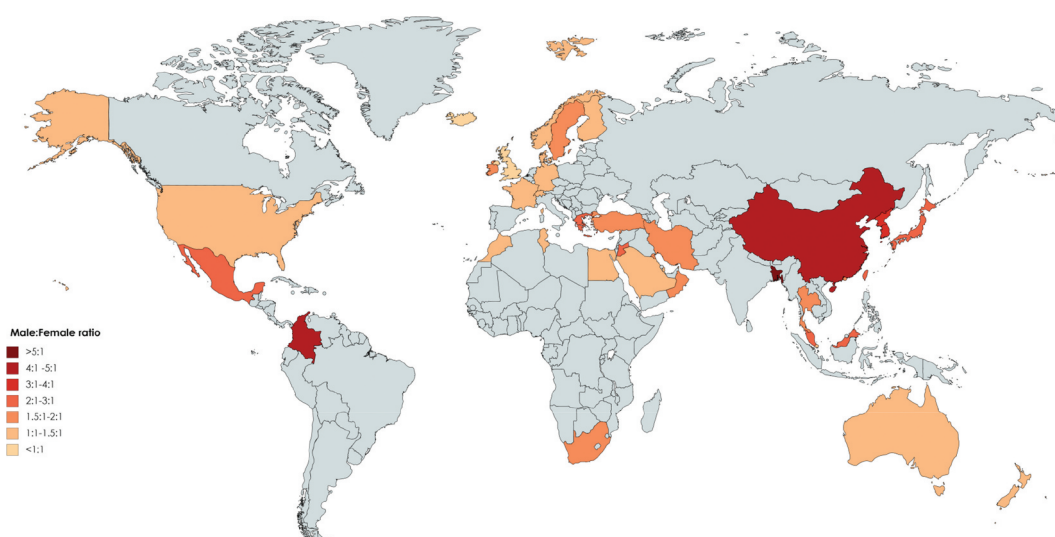


Figure 4. Proportion of male to female ratio among different registries of patients with primary immunodeficiency in the world. (Gray color represents countries without registry or without appropriate report).

from the country among 6 documenting centers represented 1837 patients in the 2014 report of the ESID registry [2]. The most recent report, however, provided a more border national view on 6392 patients when the common category of PID was predominantly antibody deficiency which was found in 69.1% of cases followed by autoinflammatory disorders (8.6%). Of note, combined immunodeficiencies occupied only 5.7% of patients in this registry. SIgAD and isolated IgG subclass deficiency were found to be the most common disorders amongst predominantly antibody deficiencies. In this registry, delay in diagnosis was calculated around 26.9 months and the consanguinity rate among reported patients was 14.3% [29,30]. Although several PID genes have been discovered in this cohort there is no national report on molecular diagnosis rate [31].

Al-Saud et al. published a registry report from Saudi Arabia with 502 patients in 2015 and identified a prevalence of all PIDs of 7.2 in 100000 children. The most common PID was combined immunodeficiencies (59.7%), followed by predominantly antibody deficiencies (12.3%) and congenital defects of phagocytosis (9.4%). T-B-SCID was the most common combined immunodeficiencies phenotype (17%). The genetic diagnosis was identified in 152 patients (30.2%) from this cohort in which consanguinity was observed in 75% [32,33].

Madkaikar et al. reported 159 PID cases from a tertiary care center in India in 2013 followed by a more recent report describing 778 registered patients. Frequencies of PIDs were as follows: diseases of immune dysregulation (23.1%), phagocytic defects (21.3%) and predominant antibody deficiency

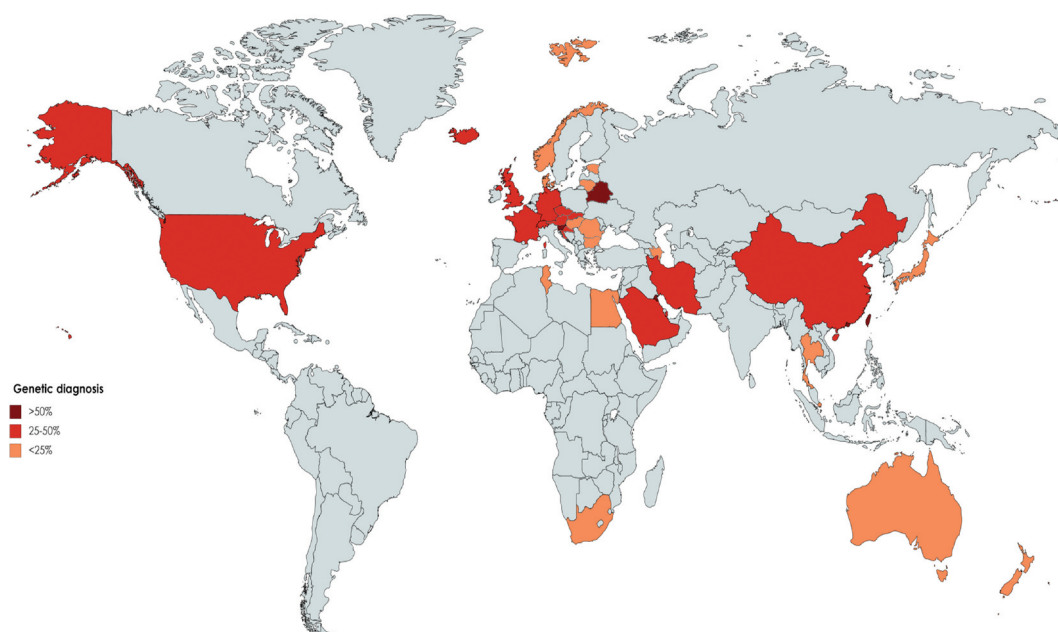


Figure 5. Proportion of molecular diagnosis among different registries of patients with primary immunodeficiency in the world. (Gray color represents countries without registry or without appropriate report).

(17.1%), Among patients molecular diagnosis was observed in 40.2% and parental consanguinity was recorded in 19.4% [34–36].

During the last decade, other Asian PID cohorts have been reported containing fewer patients each. Al-Herz et al. in 2019, published a registry report of 314 PID patients in Kuwait with the highest genetically solved rate of 69.1% with 78.0% paternal consanguinity (prevalence of PID 20.2 in 100000, predominantly antibody immunodeficiency of 17.8%) [37–39]. In 2013, Ehlayel et al. have reported a single-center registry of 131 pediatric PID patients from Qatar with the lowest number of classical PID diseases and only 23.7% predominant antibody deficiency (prevalence of PID of 1.1 per 100000 children, genetic diagnosis of 36.6%, parental consanguinity of 61.1%) [40]. Although a cohort from Hong Kong also reported 107 genetically solved PID patients, the current number of patients from this national registry is not updated and spans back to 2014 with 180 reported patients [41–43]. Rhim et al. have reported 152 PID patients from Korea up to 2012 with an estimated prevalence of 1.1 per 100000 children with the highest rate of males to females with PID in Asia (~3.6) [34]. Other registries were reported from Oman (140 patients with high proportion of patients with congenital defects of phagocyte 35%) [44], Taiwan (215 patients with 50.6% molecular diagnosis) [13], Malaysia (150 patients) [43,45], Thailand (67 patients) [46], Jordan (53 patients) [47], Singapore (39 patients) [48], UAE (30 patients) [49] and Bangladesh (13 patients) [50].

3.2. Oceania

PID registries in Oceania have been published only from Australia and New Zealand. The first publication was specific to Australia with 534 reported cases in 1997 [9] and the most recent report included both Australia and New Zealand

published by Kirkpatrick et al. including 1209 cases in 2007 (Table 1, Figures 1–5). The prevalence of PID was estimated at 5.6 per 100000 for Australia, 12.4 for the state of South Australia, and 4.9 for both Australia and New Zealand. The most frequent subcategory of PID was predominately antibody deficiency syndromes (77.4%), followed by combined immunodeficiency (8.9%), hereditary angioedema (4.5%), and defects of phagocyte function (32%). CVID was the most frequent diagnosis (38.4%) of all patients and the genetic diagnosis was established in 223 patients (18.4%) [12].

3.3. Africa

As the highest estimation, 4509 patients have been recorded in Africa mainly from 7 countries (Table 1, Figures 1–5). Initially, South African investigators published a series of PID patients at a single children's hospital in Cape Town. Patients had been diagnosed for 14 years (between 1983 and 1996). The most frequent disorder of 93 total patients was antibody deficiency (59%) and the delayed diagnosis was noted in majority of patients [51]. Later, in 2011, Naidoo et al. updated this data to span a period of 27 years from 1983 to 2009 with 168 patients. Again, antibody deficiency predominated (50.6%) and the second most common disorder was combined immunodeficiency (25.0%). A family history of PID was observed in 11% of the patients and consanguinity was reported only in 1.1% of the cases. Molecular diagnoses were archived in 7.7% of the cohort [52].

In 2015, Mellouli et al published a Tunisian nationwide registry of 710 PID patients spanning 25-years, thus representing the largest national cohort of the continent. The observed prevalence was 4.3 per 100000 in the population. The frequency of combined immunodeficiency disorders was 28.6%, followed by congenital defects of phagocyte (25.4%) and other well-defined

immunodeficiency syndromes (22.7%), and antibody deficiency disorders (17.7%). The consanguinity rate of parents was 58.2% and a genetic diagnosis was identified in 13.8% [53].

Egypt was the second country to establish a PID registry in Africa; Reda et al. published a single-center study of PID patients in 2009 with 64 patients. Antibody deficiency with 35.9% of cases was reported as the most abundant group of PID and combined immunodeficiencies were the second common PID category (29.7%). Consanguinity was reported in 62.5% and the diagnostic delay was 29.9 months [54]. Recently updated records from the Maghreb registry demonstrated that the registered patients in the country have risen to 476 with 106 molecularly diagnosed patients (22.2%) [49,55].

The PID registry next to emerge in Africa was from Morocco; Bousfiha et al. reported 424 PID patients registered by 2014. The reported prevalence of PID was 0.81 in 100,000 inhabitants. The most prevalent disorders were reported as follows: well-defined immunodeficiency syndromes (27.4%), antibody deficiencies (22.7%) and combined immunodeficiencies (20.6%). Furthermore, agammaglobulinemia accounted for the majority of antibody deficiencies patients (54.7%) and MHC class II deficiency was reported in 41.2% of combined immunodeficiencies. Parental consanguinity was identified in 43.2% of cases and 19.1% of patients had a positive family history [56]. Three recent additions to the Maghreb registry have released their preliminary reports on the PID patients in Algeria, Libya and Sudan with 600, 106 and 72 patients, respectively [49].

3.4. Europe

In this section, registries of main PID disorders were collected from both published national registries of European countries (highest estimation of 40,223 patients) and the ESID registry between 1993 and 2014 (Table 1, Figures 1–5). That showed the current total patients from the ESID registry were not queried as part of this evaluation and reliance was placed on that, which could be aggregated by a systematic review of publicly available information. The first report of a European national registry was that of Luzi, et al at in 1983 who described 797 registered patients in the Italian Registry for PIDs. The most prevalent PID entity was humoral defects and SIgAD (66.6%) was found as the most frequent disease, followed by T-cell disorders (14.2%) [57]. More recently the number of Italian patients in the ESID registry has reached 1275 [2,58], but this has not been reflected in other publications from this country with no general information regarding the genetic diagnosis of all PID patients [59,60].

The largest cohort in Europe has been reported from France with 5426 patients within the ESID registry [2,58]. In the latest report from the French PID study group from 2019, 6602 patients were registered (mainly children) in the National Reference Center of PID. In this study, the total consanguinity was reported as 15% of all patients. The most common PIDs were predominantly B-cell deficiencies (42.8%) and T-cell deficiencies (17.4%), respectively. The most frequent PID diseases were CVID (22.8%) and the molecular diagnosis was established in 43.3% of cases [61,62].

Closely following France in magnitude, Shillitoe et al. reported 4758 registered patients from 2008 to 2018 in the United Kingdom PID Registry, suggesting a doubling of the size of cohort compared to previous ESID registry report in 2014. Antibody disorders formed the largest group (59.6%) of registered patients. The most frequent diseases of PIDs were CVID (36.3%), hereditary angioedema (8%) and agammaglobulinemia (5.4%). Consanguinity was reported at 2.9% and a genetic diagnosis was confirmed in 25.3% of the cohort [63–65]. Abuzakouk, et al at in 2005, registered separately 115 patients from 1996 to 2003 within a national registry for PIDs in the Republic of Ireland (higher than those in the ESID registry 2014 with 107 patients). The most prevalent PID entities were immunoglobulin deficiencies (46%) and complement deficiencies (27.8%). The most common diseases were CVID (24.3%) followed by X-linked agammaglobulinemia (21.1%) and C1 inhibitor deficiencies (13.9%) [66].

In 2005 the Polish Working Group for Immunodeficiencies (PWGID) was established and in their first report in 2016, with 4099 recognized PID patients in Poland, demonstrating a prevalence of 10.6 per 100,000 with a dominance of antibody deficiencies (70.2%) representing the largest cohort among Eastern European countries [67].

The next largest registry in Europe belongs to Germany. El-Helou, et al reported 2453 registered patients spanning 2004 to 2019 in a national registry for PIDs [68], the current data within the ESID database, however, has presented to 1981 cases. In this national registry, consanguinity was reported in 8.0% of the total number of patients and antibody deficiencies formed the largest PID group (56.76%). The most frequent diseases of PIDs were CVID (29.6%), followed by hypogammaglobulinemia (13.5%) and the genetic diagnosis was achieved on 43.3% of patients [69].

Matamoros et al. reported 2030 registered patients in the Spanish national registry for PIDs from 1993 to 2001. According to the ESID registry, the number of reported patients has reached 2211 in 2014 [2,58]. The most prevalent category in this country was antibody disorders (69.1%) mainly due to SIgAD (36.9%) and CVID (19.9%) [18].

Sweden also reported 2727 registered patients in 2019 (most notably with antibody deficiency and phagocytosis disorders, 43.3% and 13.8% respectively) [70,71]; however, due to the inconsistency with the ESID registry, there are only 92 patients included in the continent registry [63,64]. Similarly, other Nordic countries also reported their registries of PID patients separately from ESID registry including Iceland with 66 patients (39.4% antibody deficiency, 33.3% genetic diagnosis, with the highest estimated prevalence of PID in the world ~18:100,000) [72], Norway with 372 patients (50.8% antibody deficiency, 8.8% genetic diagnosis) [10,73], Denmark with 179 patients (100% antibody deficiency, 1.6% genetic diagnosis) [74] and Finland with 132 patients (100% antibody deficiency, although in the recent report they did not include previous Finish patients with other PID entities) [75].

Registries from Croatia (226 vs. 24 patients), Czech (518 vs. 259 patients), Portugal (208 vs. 76 patients), Slovenia (272 vs. 16 patients), Slovakia (227 vs. 63 patients), Estonia (99 vs. 42 patients), Belarus (436 vs. 67 patients), Romania (222 vs. 11 patients), Lithuania (172 vs. 8 patients), Hungary (730 vs. 404

patients), Austria (312 vs. 105 patients), Azerbaijan (100 vs. 0 patients), Bulgaria (113 vs. 0 patients), and Israel (294 vs. 4 patients) are not updated in the ESID database and therefore national publications were referred to for the most accurate estimation. In contrast, the ESID registry is the only source for extraction of nationally diagnosed PID patients in many Eastern European countries including Serbia (88 patients), Ukraine (33 patients), as well as the most updated data from Belgium (258 patients), Greece (202 patients), Russia (204 patients), Switzerland (352 patients) and the Netherlands (743 patients) [2,58,76] for which it has been included in these analyses as such (Table 1).

3.5. North and South America

The first registry in the United States dates back in 1993 and the first report of this initiative was published in 2000 with only 368 patients. Afterward, following the formation of United States Immunodeficiency Network (USIDNET) for developing a research consortium to advance research in the field of PID, the recent output from their online website presented in 2020 described 5484 diagnosed patients (45.8% genetically diagnosed). The most common diseases of PIDs were CVID (35%), IgA deficiency (26%), IgG subclass deficiencies (9%) and SCID (9%) [77]. Moreover, based on the JMF Physician Education and Public Awareness Campaign (PEPAC) in 2018, 30,227 patients in the United States were identified with specific PIDs. The patients classified within 8 major PID groups where the most prevalent deficiencies were first humoral immunodeficiencies (57.1%) and syndromic cellular immunodeficiencies were second (15.6%) [78]. The same data source from PEPAC shows the data registered from Canada from where 3047 patients have been documented, although detailed data on the PID category and genetic diagnosis has not yet been published from this country [78].

In a parallel effort, the LASID was established in 1993 and their first report was published in 1998 with collected information on a total of 1428 patients from eight countries [79,80]. They later have issued their second report in 2006 with 3321 patients registered from 12 countries and their online evaluations demonstrated that currently 18 countries are included with a total number of 8146 patients. It was reported that 53.0% had predominantly antibody deficiency and 22.6% had other well-defined PID syndromes as the main disease categories of the region. Genetic diagnosis has been made in 18.0% of the registered patients [16,81–85].

The main registered patients of the LASID are from four national registries with more than 1000 patients including Argentina, Brazil, Mexico and Colombia. Nestor et al reported 1319 PID patients from Argentina in 2007 which has now risen to 2730 patients in the LASID database. Reported frequencies were as follows: humoral (69.5%), phagocyte (4.3%), cellular (3.94%) and complement defects (1.4%). Grumach et al. in 1997 reported data on 166 PID patients over 15 years referred to as a national center in Brazil. Now with 1879 patients, this national cohort stands as the second largest of the region where predominantly antibody deficiencies (60.8%), T cell defects (4.9%), and phagocyte disorders (18.7%) are the main PID categories [86]. SIgAD was recorded in 25.1% and CVID in

20.3% of patients within this registry [87]. Mexico had 1744 patients (36.3% antibody deficiencies) and Colombia had 1073 (46.2% antibody deficiencies) patients, each as of prominent countries of the LASID registry that report their outcomes separately [83,84]. Table 1 represents the PIDs epidemiologic indexes based on reported cases of national and international registers of North and South American countries with an estimated 42067 patients.

4. Discussion

Via systematic review, we considered all evidence of publicly available PID registries world-over based on national reports from 80 countries as well as all well-known international registries. We considered certain clinical parameters and background factors including frequency of specific PIDs, country-specific prevalence, and percentage of consanguinity. Reports from the PID databases of different countries provide an opportunity to understand regional features and epidemiology of PID globally as well as identifying reasons for clinical and epidemiological variations on different continents. Moreover, through the current exercise, we can evaluate previous measures as well as the global report from JMF and highlight potential underestimation and underreporting in different regions [88].

Asia is the most populous continent with 48 countries, but only 18 of them (37.5%) have the reported data of PID registries. It is notable that nearly half of these countries have not established a national registry, but many do have published PID data from single large medical centers including Qatar, Oman, Korea, Thailand and India which make these data relatively unreliable as prevalence estimates. However, this shortcoming to some extent may be overlooked in small and low population countries, but the global estimation of PID is challenged by these types of data originating from large countries such as China and India [89]. Despite limitations in data, the spectrum of the prevalence of PIDs varies from a low of 0.08:100000 in Bangladesh to a high of 20.2:100000 in Kuwait. Collectively, Middle Eastern countries show higher PID prevalence than other countries from Eastern Asia probably due to higher percentages of parental consanguinity. There were also vast variations in the prevalence of individual PIDs throughout the continent. Predominantly antibody deficiencies were the most frequent subcategory of PID in East Asian countries which is parallel to results of Australia [90], LASID [81] and ESID [11] databases, and also the JMF network (55%) [78], but this percentage was lower in the cohorts from the Middle East (Figure 3). Combined immunodeficiencies were the most common PID entity in Saudi Arabia (59.7%) and the second most prevalent group of PID in other Middle Eastern countries such as Iran [91], and Kuwait [92], which are all much higher than the ESID, LASID [81] and other Western registries [8,11,18,57], Far-East countries [14,27,45], and Australia [12]. This finding is likely explained by the considerable rate of the parental consanguinity which is reported from the Middle East [32,54,91,92] and related to a high rate of autosomal recessive forms of PIDs [93–96]. The latest JMF data describe 8022 patients from Asian countries and thus this global registry has a gap of 7917 patients from currently

reported national registries (Table 1) demonstrating what is likely to be the partial capture of that network [88].

Diagnostic delay, which is defined as the elapsed time between the onset of PID symptoms and the establishment of diagnosis, can reflect the awareness of PID among physicians and the public. The lowest was reported in Iran with a median of 12 months and the highest was in Malaysia at 3.78 years. There was also an increased male to female sex ratio in all registries, but it was greater than 2 in Thailand, Korea, Malaysia, China and Japan suggesting a greater prevalence of X-linked transmission (Figure 4). Asian countries report a 25.9% molecular diagnostic rate which is the highest globally and is mainly attributed to the Middle East countries (Table 1, Figure 5).

Oceania is comprised of Australasia, Melanesia, Micronesia and Polynesia and has a population of 43 million living in 15 countries. Reporting of PID patients, however, is available only from 2 countries (13.2%). Although the regional report presented 1209 patients, the recent JMF global report described 1876 patients from this region indicating the need to update registry reported data from Oceania, probably with the inclusion of countries included in the JMF network but otherwise not part of regional registries. Of note, Oceania has an appropriate percentage of genetic diagnosis compared to other continents with 11.8% of reported patients (Table 1) [88].

Africa accounts for near 15% of the global population [97], but of its 54 countries, only 7 (12.9%) have published registries of PID patients. Furthermore, only Tunis, Morocco and South Africa have established countrywide registries and thus there is not enough experience to establish a continent-wide landscape of PID for Africa [98]. The recent establishment of the Maghreb registry and African Society of Immunodeficiency (ASID), however, could change this condition in the near future [49,98,99]. The reported prevalence of PID in African countries seems to be underestimated due to the general lack of awareness and knowledge of immunodeficiencies, however, a comparison with the JMF global report in which there were only 1836 patients to the 4509 now reported patients in the Maghreb registry suggests progress is accelerating (Table 1) [88]. Only 5.5% of all reported patients demonstrated a molecular diagnosis, the lowest continental rate globally. However, in North African countries, the appearance of autosomal recessive forms of PID is more frequent and is likely a result of consanguinity (Figure 2). The pattern of PID in North Africa (mainly with higher percentages of combined immunodeficiency), however, is dissimilar from that identified in South Africa (Table 1, Figure 3), possibly owing to higher rates of endogamy, geographical alteration, as well as genetic differences. Moreover, differences can be the result of variable data collection methods and awareness of PIDs between African countries.

As of 2014 the ESID registry contained 19355 patients and represented the most robust initial effort in registration. The database, however, does not cover all 51 European countries (58.8%, mainly missing from Nordic countries), although the estimation of the 2019 database reaches 25023 cases (including Turkish patients) [2,58] and 33503 cases on their online

website [100]. The current systematic review, however, estimates several missing patients in the registry from individual national reports (Table 1). Compared to the JMF global report with 40223 patients from Europe [88], a gap of over 6720 patients is apparent and thus efforts to pursue and integrate data from the missing countries are pressing [69,76,101]. Adaptive immune deficiencies due to predominantly B-cell deficiencies encompass the main category of PIDs in Europe (Figure 3) [61]. Based upon the national registries of European countries, Iceland with its well documented universal medical system reported the highest prevalence of PIDs globally. This has been hypothesized to be due to a sparse population and a small denominator which might skew the comparison to larger nations [72]. However, all Nordic countries cover accessible and universal healthcare, while they also have regional enrichment of rare variants due to previous 'genetic bottlenecks'. This has led to the enrichment of so-called founder mutations in various monogenic autosomal recessive genes [102,103]. Also, the legislation of most Nordic countries does not presently allow for data exchange with cross-border registries. This does not serve the needs of rare disease patients nor follow the principles behind European General Data Protection (GDPR). According to GDPR, personal data should be designed to serve mankind. The right to the protection of personal data is not absolute; it must be considered in relation to its function in society and be balanced against other fundamental rights (e.g. equity, freedom of science, social rights, the duty of the society to promote public health), following the principle of proportionality [104]. Comparison with other European countries suggests that on average 5:100000 is a reasonable estimation for the PID prevalence in Europe as a whole [5,10,105,106].

Overall, among European countries included in the ESID database, CVID composed approximately 55% and was the most prevalent PIDs registered, whereas, in older studies performed, SIgAD was more commonly reported. The proportion of CVID is lower in France than reported by national registries than in other European countries such as Germany and the UK. There was also a relatively low observed prevalence of PIDs in adults in France. For the five European countries that reported patient consanguinity, France had the highest with 15% along with a concomitant increase of PIDs with an autosomal recessive inheritance pattern (Figure 2). In general, national European registries reported average consanguinity of 3.4%. Moreover, based on reported cases in the ESID database performed by Gathmann, et al at 2011 [107] focused on eight countries including France, Spain, Turkey, United Kingdom, Germany, Italy, Poland and Netherlands consanguinity was reported in 8.8%, and 18.5% of patients were reported to be familial cases. Genetic diagnosis is only 15.5% of clinically diagnosed patients with Belarus leading (57.3% definite diagnosis) followed by Slovenia (57.0% definite diagnosis) and France (40.0% definite diagnosis, Figure 5). The discrepancy amongst European countries suggests substantive opportunity to more broadly advance genetic diagnosis in Europe [76].

Unlike prevalence estimations in many countries based upon their registry reports and diagnosed cases, in the

United States, PID epidemiological indices were estimated via a very large geographically and racially diverse population. The USIDNET provides one of the most updated and advanced platforms of evaluation of patients in the country, but a recent report from JMF showed that the participant centers in this database were incomplete (5484 vs. 30227, 24743 missing patients) [88,108]. Moreover, the JMF registry is the only one that covers PID in Canada, a country with 37 million inhabitants and 3047 patients. In contrast, the estimates from Latin American countries via the LASID database are more consistent with data presented in the JMF global report (8146 vs. 8793; only 647 missing patients) [82,88]. Reports from collaborative LASID countries demonstrate that in Latin America the most frequent form of PID is predominantly antibody deficiency, but less frequently than that observed in North America. Other observed differences, however, such as high numbers of patients with CID and MHC class II deficiency in Costa Rica's and Peru and DiGeorge syndrome in Chile require further evaluation (Table 1). The comparison of PID prevalence (5:100000 vs 2:100000) and genetic diagnostic percentages (45.8% vs. 18.0%) between North American countries and Latin American countries emphasizes a requirement for in-depth efforts to improve the PID registration quantity and quality.

5. Expert opinion

While many PIDs can be easily diagnosed and have effective treatment options available, awareness of PIDs and their management is low amongst both physicians and the general public in many countries leaving numerous patients undiagnosed. The number of undiagnosed cases is not known, however, because there is no population-based screening process for PID except newborn screening for SCID in certain countries. However, in the present systematic approach as shown in Table 1, we estimated possible reported patients of 104614 based on registry reports and diagnosed cases that represent at least 10590 missing patients compared to the JMF global report [88]. The Jeffrey Modell Centers Network (JMCN) consists of 821 Expert Physicians at 379 institutions, in 294 cities, and 86 countries spanning 6 continents. The JMF registry compiles significant data received directly from these reporting Centers from around the world. Of note, the number of individual country registries included in the analysis for each region in this systematic review may not be the same as the number of countries included in the JMF registry for each region. Similarly, the specific countries reporting may vary as well. Still, this number based on registrations remains underestimated as if we simply calculated the incidence of SCID disorders using estimates from newborn screening (1:50000 individuals in a non-consanguineous population [109]) there should be at least 1540000 SCID patients worldwide. Several studies attempted to estimate the total number of PID patients based on hospital and population-based measurements [37]. The upper estimates suggest 6–8 million people may be living with a PID worldwide (based on US population and hospital prevalence [77,110]). It is also estimated that more than 700000 new PID patients might be diagnosed annually (based on US population incidence [111]). In line

with the total number of patients we reported based on our systematic review, the majority of experts in the PID filed reported that unfortunately a large portion of PID patients (70–90%) remain undiagnosed and do not have access to appropriate treatment, even in countries with existing PID facilities (the National Institutes of Health [NIH] estimates that as a group, PID may affect 1–2% of the population) [37,112]. The main reasons for high rates of undiagnosed PID patients include a low level of awareness of symptoms of PID among physicians, failure to consider this diagnosis and differences in diagnostic capabilities and treatment of PIDs from country to country on different continents and even within the same region [113]. It should be noted that many PIDs can be diagnosed easily with two simple blood tests (whole blood counts and immunoglobulin levels which diagnose antibody deficiencies and classical immunodeficiencies with a severe lack of lymphocytes or granulocytes) [114]. Prompt PID diagnosis results in better use of health facilities, surveillance of the risk that PID patients can expose for society (e.g. reservoir of Poliovirus challenging the Polio Eradication program [115]) and has been demonstrated to result in lower healthcare costs overall [116].

Both this systematic review and the JMF global report are in agreement that antibody deficiency (51.9% vs. 45.1%, respectively) and combined immunodeficiency (11.8% vs. 6.1%, respectively) are the most often reported PIDs in the world. The number of males affected by PID is slightly higher than females, according to both systematic review and JMF global report (1.5 vs. 1.3, respectively) representing the significant role of X-linked PID disorders in all registries except the UK and Iceland (Table 1, Figure 4). Parental consanguinity was positive in 6.2% of patients which is less than current estimates of global populations in the world (20%) [117], indicating the low contribution and presence of established PID registries in the countries with consanguinity (Figure 2). Where present, however, parental consanguinity demonstrates the increased frequency of autosomal recessive PID. In total, 13.2% of patients received a final molecular diagnosis demonstrating the shifting landscape of PID globally (Figure 5). In an effort to increase the molecular identification of PID patients and significantly increase the genetic diagnostic rate, the JMF is about to embark on a global genetic sequencing initiative. Their current data on global gene defects associated with PID showed that the chromosome 22q11.2 deletion syndrome (5215 cases), MEFV deficiency (2835 cases) and ATM deficiency (2514 cases) are the most common genetic defects worldwide [88]. Collective information and reports on variants are important for long-term therapeutic strategies based on countries or geographical regions. This initiative aims to provide accurate diagnoses, leading to appropriate management and treatment, and ultimately improved patient outcomes and quality of life [118]. Recruitment strategies of PID patients in the national and continent based cohorts should be revised to detect quicker patients with multidisciplinary care for patients presenting different types of infectious or noninfectious complications. Moreover sustainable funding should be provided for long-term maintenance of the currently available databases (societies, registries and websites) and to support highly specialized therapies (e.g. JMF and RITA European research

network) [88,119]. Although current data presented cover registries only from 80 countries, the JMF report covers more than 86 countries demonstrating the higher potential for the registry which should be pursued to improve current understanding of PID and increase the chances for improved management. The global burden of PID is clearly underestimated and improved registration efforts could help in more accurately estimating the burden of the disease and allowing for the allocation of appropriate resources for these complex heterogeneous genetic disorders.

Author contributions

- (1) The conception and design of the study
- (2) Acquisition of data,
- (3) Analysis and interpretation of data,
- (4) Drafting the article
- (5) Revising it critically for important intellectual content,
- (6) Final approval of the version to be submitted

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Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

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